

The blink reflex recovery cycle differs between essential and presumed psychogenic blepharospasm

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ABSTRACT

Background: Psychogenic blepharospasm is difficult to distinguish clinically from benign essential blepharospasm (BEB). The blink reflex recovery cycle measures the excitability of human brainstem interneurons and is abnormal in BEB. We wished to study the blink reflex recovery cycle in patients with atypical (presumed psychogenic) blepharospasm (AB).

Methods: This was a prospective data collection study investigating the R2 blink reflex recovery cycle at interstimulus intervals (ISI) of 200, 300, 500, 1,000, and 3,000 msec in 10 patients with BEB, 9 patients with AB, and 9 healthy controls. All patients had spasm of the orbicularis oculi muscles. To compare individual patients, an R2 recovery index was calculated as average of the recovery values at ISIs of 200, 300, and 500 msec, with the upper limit of normal defined as mean (control group) + 2 SD.

Results: The R2 recovery cycle was significantly disinhibited in patients with BEB, whereas patients with AB did not differ from controls on a group level. The upper limit of normal for the R2 recovery index was 61%. The R2 index was abnormal in 9 out of 10 patients with BEB and in none of the patients with AB.

Conclusions: A normal blink reflex recovery cycle indicates normal brainstem interneuron excitability. Assessment of the R2 recovery cycle may provide a useful diagnostic tool to distinguish patients with psychogenic blepharospasm from BEB and is worthy of further study. *Neurology*® 2011;76:610-614

GLOSSARY

AB = atypical (presumed psychogenic) blepharospasm; **ANOVA** = analysis of variance; **BEB** = benign essential blepharospasm; **ISI** = interstimulus interval; **PB** = psychogenic blepharospasm; **PMD** = psychogenic movement disorder.

Primary or benign essential blepharospasm (BEB) is a focal dystonia characterized by excessive involuntary closure of the eyelids not due to a secondary cause.^{1,2} Disease onset is in later life (mean 55.7 years) and it is 2.3 times more common in women.^{3,4} Typical BEB is a bilateral condition and strong light can worsen eye-closing spasms while anxiety or enhanced attention can paradoxically improve them.

Estimates of psychogenic blepharospasm (PB) vary between 0.3% and 7% of all psychogenic movement disorders.⁵⁻⁷ In our clinical practice, we often observe patients with atypical features to their blepharospasm, such as a relatively young age and acute onset, constant eye closure, unusual aggravating or relieving factors, or unusual (sometimes immediate) response to botulinum toxin injections. Although one would expect such features to be more typical for PB, establishing a final diagnosis is sometimes difficult on clinical grounds alone. Patients with presumed PB often only have a low level of evidence for a psychogenic movement disorder (PMD).⁶⁻¹⁰ In addition, in typical BEB, confounding clinical features such as variability and distractibility, as well as improvement with concentration and anxiety, may be present; patients with BEB may also have psychiatric comorbidity.¹¹ Therefore, an objective test to help distinguish between essential and psychogenic blepharospasm would be of clinical utility.

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Supplemental data at
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The R2 blink reflex recovery cycle is an electrophysiologic measure of brainstem excitability and is known to be abnormally enhanced in BEB caused by contraction of the orbicularis oculi muscles.^{12–14} It is normal in patients with apraxia of eyelid opening.^{15,16} We hypothesized that patients with atypical (presumed psychogenic) blepharospasm would have a normal blink reflex recovery curve and therefore differ from BEB.

METHODS Participants. Among a total of 50 consecutive patients with blepharospasm who were seen between July 2008 and June 2009 in our botulinum toxin injection clinic, we identified 11 (22%) with atypical clinical features such as acute mode and early age at onset, constant eye closure, persisting unilateral

or asymmetric symptoms, paroxysmal symptoms, and other inconsistencies such as pain, associated somatizations, abolishment of blepharospasm with distraction, unusual sensory tricks, or unexpected response to botulinum toxin injections and suggestion.

Nine out of 11 patients with AB (aged 47 to 68 years) agreed to participate in the blink reflex study. Out of these 9, 2 had a clinically definite, 6 had a probable, and 1 had a possible PMD (table e-1 on the *Neurology*® Web site at www.neurology.org).^{5,6} We also recruited 10 consecutive patients with BEB, 5 of whom had spread to other craniocervical body parts (aged from 58 to 75 years) and 9 healthy control subjects (aged from 47 to 69 years). The diagnosis of AB as well as BEB was given by one movement disorders specialist (K.P.B.) who was also involved in the treatment of these patients. All patients with AB and BEB had involuntary discharges in the orbicularis oculi muscles. All subjects had stopped any drugs that would potentially act on the CNS for at least 24 hours, and the last injection with botulinum toxin had been given at least 3 months before the study.

Standard protocol approvals, registrations, and patient consents. Before inclusion in the study, written informed consent was obtained from all participants. This study was approved by the Joint Research Ethics Committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology, London, UK.

Clinical assessment. Information regarding demographics, medical and family history, disease course, and treatment were collected during a face-to-face interview. We assessed symptom severity using the Jankovic Rating Scale¹⁷ and the Blepharospasm Disability Index.¹⁸ Clinical data were collected prior to the assessment of the blink reflex recovery cycle. If appropriate, patients received their regular botulinum toxin injections after the study and were asked to complete the Blepharospasm Disability Index and the Patient Evaluation of Global Response¹⁹ after 3 weeks.

Blink reflex and R2 blink reflex recovery cycle. Surface EMG recordings were made from the orbicularis oculi muscle of the more affected side (left side, if symptoms were symmetric) using Ag-AgCl surface electrodes. The EMG signals were amplified using D360 amplifiers (Digitimer, Welwyn, UK), bandpass filtered (53–2,500 Hz), analog-to-digital-converted using a 1401 AD converter (CED, Cambridge, UK) at a sample rate of 5,000 Hz, and collected on a computer. Electrical stimulation was applied to the supraorbital nerve in the supraorbital notch with a bipolar stimulating electrode and constant current generator (Digitimer). All stimuli were 0.2 msec duration and stimulus intensity was set at 3 times R2 threshold (lowest intensity with an R2 response in at least 5 out of 10 trials). Subjects were studied at rest, with eyes gently closed. The blink reflex in response to paired stimulation was assessed at interstimulus intervals of 200, 300, 500, 1,000, and 3,000 msec (6 trials each, pseudorandomized). Pairs of stimuli were separated by varying time intervals of 20–40 seconds to minimize habituation. Trials with excessive EMG artifact were rejected online. Data were analyzed offline using Signal software (Cambridge Electronic Design, UK). The raw blink recordings were DC-corrected, rectified, and averaged. The onset latency and duration of R1 and R2 responses were determined by manual cursor marking of the beginning and end of responses. The area of the conditioned R1 and R2 was calculated over the same duration as the unconditioned response. The area ratio of the conditioned R1 and R2 components to the unconditioned responses was calculated. We additionally calculated an R2 recovery index in each subject as

Table 1 Demographics and clinical characteristics

	BEB (n = 10)	AB (n = 9)	Significance level, p < 0.05
Female: male	9:1	6:3	
Age at onset, y, mean (SD)	55.2 (12.6)	47.3 (6.8)	NS
Disease duration, y, mean (SD)	11.7 (10.3)	7.2 (7.7)	NS
Family history, n (%)	3 (30)	1 (11)	NS
JRS (max 8), mean (SD)	5.7 (1.6)	6.2 (1.4)	NS
BDI (max 4), mean (SD)	2.3 (0.6)	2.2 (0.9)	NS
BDI change 3 weeks after Botox, mean (SD)	1.0 (0.9)	0.9 (0.6)	NS
Global response (–4 to +4), mean (SD)	2.2 (1.3)	2.3 (1.6)	NS
Mode of onset, n (%)			p = 0.001
Abrupt	0 (0)	7 (78)	
Gradual	10 (100)	2 (22)	
Precipitating event, n (%)	2 (20)	3 (33)	NS
Precipitating eye symptoms, n (%)	6 (60)	3 (33)	NS
Asymmetry, n (%)	0 (0)	3 (33)	NS
Remissions, n (%)	0 (0)	3 (33)	NS
Spread, n (%)	6 (60)	4 (44)	NS
Photophobia, n (%)	7 (70)	6 (67)	NS
Sensory trick, n (%)	4 (40)	1 (11)	NS
Distractibility, n (%)	0 (0)	3 (33)	NS
Chronic treatment with botulinum toxin, n (%)	10 (100)	5 (56)	p = 0.033
Duration of botulinum toxin treatment, y, mean (SD)	9.1 (8.7)	4.4 (6.5)	NS
Dose of botulinum toxin, units, mean (SD)	92.8 (35.6)	63.3 (79.7)	NS
Response to botulinum toxin, n (%)			p = 0.02
As expected	9 (90)	3 (33)	
Not as expected	1 (10)	5 (56)	
Immediate response	0 (0)	2 (22)	
No response	1 (10)	3 (33)	
NA	0 (0)	1 (11)	

Abbreviations: AB = atypical (presumed psychogenic) blepharospasm; BDI = Blepharospasm Disability Index; BEB = benign essential blepharospasm; JRS = Jankovic Rating Scale; NA = not applicable; NS = not significant.

Table 2 Blink reflex results^a

	BEB	AB	Controls	p Value
Sensory threshold, mA	1.6 (0.4)	2.0 (0.8)	1.7 (0.4)	0.248
Stimulation intensity, mA	9.6 (2.1)	11.7 (4.9)	10.8 (5.5)	0.568
R1 area, mV.s	0.00020 (0.00018)	0.00037 (0.00019)	0.00049 (0.00026)	0.024 ^b
R1 latency, ms	10.03 (0.78)	10.48 (0.75)	10.43 (0.68)	0.367
R1 duration, ms	9.64 (3.42)	9.56 (0.99)	11.45 (2.89)	0.254
R2 area, mV.s	0.0014 (0.0012)	0.0038 (0.0018)	0.0033 (0.0016)	0.006 ^b
R2 latency, ms	35.8 (3.3)	34.3 (2.1)	34.6 (2.5)	0.440
R2 duration, ms	47.3 (5.7)	48.6 (9.3)	49.1 (6.6)	0.854

Abbreviations: AB = atypical (presumed psychogenic) blepharospasm; BEB = benign essential blepharospasm.

^a All values are given as mean (SD).

^b Indicates significance at a 5% level.

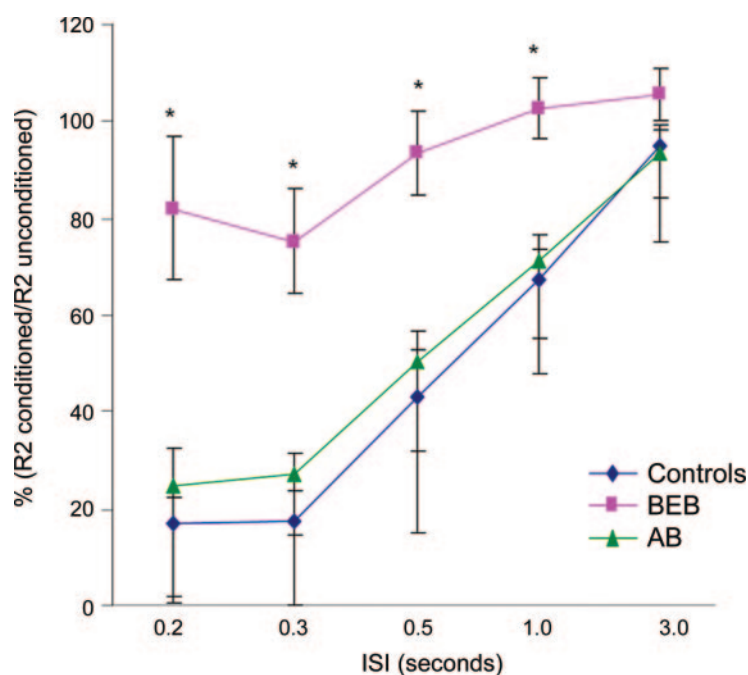
the mean of R2 area ratio values at ISIs of 200, 300, and 500 msec. The upper limit of normal for R2 area recovery index was defined as the mean + 2 SD of data from healthy controls.

Statistical analysis was performed using SPSS 16.0. Data from the 2 patient groups and control subjects were compared using one-way analyses of variance (ANOVA) for R1 and R2 area, latency, and duration. To assess R1 and R2 recovery curves, a mixed-model ANOVA was performed with ISI as within-subject factor (200, 300, 500, 1,000, and 3,000 msec) and group as between-subject factor. Post hoc *t* tests with Bonferroni cor-

rection for multiple comparisons were used to explore the nature of significant effects and interactions found in the ANOVA.

RESULTS Information regarding demographics, history, and clinical characteristics of patients with BEB vs AB is given in table 1. Table 2 summarizes the results of the blink reflex study.

In healthy controls and in both patient groups, unilateral electrical stimulation of the supraorbital nerve evoked an early response (R1) followed by a late response (R2) in the orbicularis oculi muscle. All subjects tolerated the assessment without any problems and with no adverse events. We computed separate one-way ANOVAs to compare sensory threshold, stimulation intensity, area, latency, and duration of R1 and R2 of the unconditioned stimulus between the groups (table 2). There was a difference between the groups regarding R1 area ($F_{2,25} = 4.339$; $p = 0.024$) and R2 area ($F_{2,25} = 6.230$; $p = 0.006$). Post hoc *t* tests with Bonferroni correction showed that controls had a larger R1 area ($p = 0.022$) and R2 area ($p = 0.038$) compared to BEB. Patients with AB had a larger R2 area ($p = 0.009$) compared to BEB. The latency and duration of unconditioned R1 and R2 responses were similar in all 3 groups.

Figure 1 Blink reflex recovery cycle

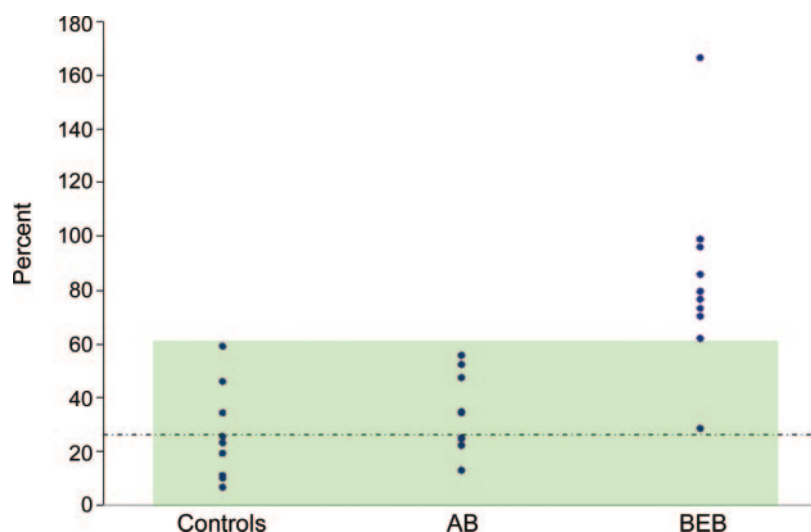
Blink reflex recovery cycle of the R2 component (area) in controls and patients with benign essential blepharospasm (BEB) and atypical (presumed psychogenic) blepharospasm (AB). Means are shown for the ratio of the conditioned R2 component to the unconditioned response. Error bars represent standard errors for the estimated least-squares means. *Significant difference between BEB vs controls and AB at a 5% level. X-axis: interstimulus intervals (ISI) in seconds. Y-axis: ratio of the conditioned to the unconditioned R2 response in percentage (%).

R1 blink reflex recovery curve. Mixed-model ANOVA with ISI as within-subject factor and group as between-subject factor showed an effect of ISI ($F_{2,4,61} = 5.539$; $p = 0.004$), but no significant effect of group or the ISI and group interaction. This was due to a difference ($p < 0.04$) between ISI of 300 compared to ISIs 500, 1,000, and 3,000.

R2 blink reflex recovery curve. Mixed-model ANOVA with ISI as within-subject factor and group as between-subject factor showed an effect of ISI ($F_{2,6,64} = 61.728$; $p < 0.001$), of group ($F_{2,25} = 16.241$; $p < 0.001$), and of the ISI and group interaction ($F_{5,1,64} = 4.391$; $p = 0.002$). This was explained by an enhanced recovery of the R2 component in patients with BEB compared with control subjects ($p < 0.001$) and patients with AB ($p < 0.001$) (figure 1). The suppression of the conditioned R2 component in patients with BEB was less at intervals 200 msec, 300 msec, 500 msec, and 1,000 msec ($p < 0.004$ for all intervals) compared to healthy controls and to patients with AB. No significant differences were found at ISI 3,000 msec.

The upper limit of normal for R2 recovery index was 61%. The R2 recovery index was abnormal in 9 out of 10 patients (90%) with blepharospasm, and in 0 out of 9 patients with AB (0%) (figure 2). An abnormal R2 index in this study therefore identified

Figure 2 R2 recovery index in each subject



X-axis: groups: controls, AB = atypical (presumed psychogenic) blepharospasm; BEB = benign essential blepharospasm. Y-axis: R2 recovery index in percentage. The upper limit of normal for R2 area recovery index was 61% (light green area) (defined as the mean [dotted line] + 2 standard deviations [data from healthy controls]).

patients with clinically typical blepharospasm (BEB) with a specificity of 90% and a sensitivity of 100%.

DISCUSSION We have studied 9 patients with atypical (presumed psychogenic) blepharospasm. In contrast to BEB, they exhibited a normal excitability of brainstem blink reflex circuits (as measured by R2 area in the blink reflex recovery cycle). Indeed, the results separate the groups so well that the blink reflex recovery curve might prove to be useful in differentiating psychogenic blepharospasm from the idiopathic form.

Psychogenic blepharospasm is thought to be rare. In a series of 131 patients with PMD, blepharospasm or other facial movements accounted for only 0.3% (4/152) of all types of psychogenic movements⁵; in other series of PMD, 2%–7% of the cases had blepharospasm and facial movements.^{6,7} In our series, 22% of all blepharospasm patients in a tertiary botulinum toxin clinic had atypical features and were clinically suspected to have a psychogenic movement disorder. However, the level of diagnostic certainty was only possible or probable psychogenic in 7 out of 9 patients. Even if we disregard current clinical diagnostic criteria for PMD, there were very few clinical pointers that consistently distinguished atypical from BEB patients in our sample. The most discriminating clinical feature was the mode of onset, which was abrupt in 7 out of 9 atypical patients and in none of the patients with BEB. Response to botulinum toxin injections was also discriminating to some extent. There was clearly ongoing diagnostic uncertainty in relation to these patients, as 4 out of 9 patients had

received inappropriate chronic treatment with botulinum toxin injections for at least 1 year.

Previous studies have established the utility of specialized electrophysiologic techniques in aiding or confirming the diagnosis of certain PMDs and a recently proposed revision of the diagnostic classification of PMD included a “laboratory-supported definite” level (primarily in cases of psychogenic tremor and psychogenic myoclonus).²⁰ A clinical distinction between organic and psychogenic dystonia can be extremely challenging. Most electrophysiologic studies have so far focused on patients with the fixed dystonia syndrome or psychogenic dystonia affecting limb, trunk, and neck muscles. While these patients show the same abnormalities of short- and long-interval intracortical inhibition, cortical silent period, and spinal reciprocal inhibition as patients with primary dystonia,^{21,22} response to a plasticity protocol (paired associative stimulation) was abnormal only in primary dystonia.²³ These similarities and differences between psychogenic and primary dystonia have only been reported on a group level, hence their usefulness as a discriminating tool remains to be proven. There are no published data available regarding these findings in patients with psychogenic blepharospasm.

The present data confirm previous results showing an abnormally enhanced R2 blink reflex recovery curve in patients with BEB. The new finding is that the recovery curve is normal in patients with atypical (presumed psychogenic) blepharospasm. Patients with BEB had a smaller R2 response than healthy subjects or patients with atypical blepharospasm, probably because most of the patients with BEB had been receiving regular botulinum toxin treatment, which could lead to chronic denervation of the orbicularis oculi muscles. However, this is unlikely to have affected the results since botulinum toxin injections have no effect on blink reflex recovery curves in BEB.^{24,25} There was also no difference in the latency and duration of the responses nor in the recovery curve of the R1 component.

The difference between the patient groups was striking. When we calculated a mean recovery index using 3 adjacent ISIs, we found that an abnormal R2 index identifies patients with clinically typical blepharospasm (BEB) with a specificity of 90% and has a sensitivity of 100%. Therefore, an abnormal R2 index makes a diagnosis of a psychogenic blepharospasm unlikely. A normal R2 index in a patient with clinically suspected psychogenic blepharospasm (and spasm of orbicularis oculi muscles) strengthens the clinical diagnosis. Patients with solely involuntary levator palpebrae inhibition have been shown to exhibit a normal R2 recovery cycle,²⁶ hence the R2 index can only assist in distinguishing organic and psychogenic causes of involuntary discharges in the orbicularis oculi muscles.

Although the findings of our study are promising, sensitivity and specificity need to be assessed with a larger sample size before integrating assessment of R2 blink reflex recovery cycle in the routine workup of patients with clinically suspected psychogenic blepharospasm. If our finding is confirmed in a larger study population it may allow a laboratory-supported definite level of certainty for psychogenic blepharospasm.

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